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Immune Function in Breast Cancer Survivors

PRINCIPAL INVESTIGATOR: Gail Ironson, Ph.D., M.D.

CONTRACTING ORGANIZATION: University of Miami Medical School  
Miami, Florida 33136

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**6. AUTHOR(S)**

Gail Ironson, Ph.D., M.D.

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

University of Miami Medical School

Miami, Florida 33136

**8. PERFORMING ORGANIZATION  
REPORT NUMBER****E-MAIL:**

gironson@umiami.ir.miami.edu

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The objectives and specific aims of the ongoing study are to evaluate massage and relaxation therapies for an ethnically diverse group of women with early stages of breast cancer (Stages 1 and 2) for 1) decreasing anxiety, stress and stress hormones, 2) decreasing depressed mood and increasing serotonin (a biochemical that diminishes with depression) and 3) increasing Natural Killer cell number and cytotoxicity (immune measures that fight tumors and viruses). During the course of the three-year study, 60 women diagnosed with Stage 1 and 2 breast cancer will be recruited and assigned to a massage therapy (n=20), a relaxation therapy (n=20) or a control group (n=20). Women in the massage and relaxation therapies will receive 3 sessions a week for 5 weeks. On the first and last day of a 5 week period, self-report measures will be collected on anxiety and depression and women will submit a urine sample and have their blood drawn to assay treatment effects on stress hormones and immune measures. Findings thus far on a subsample of 25 women reveal that women in the massage therapy group showed 1) reduced anxiety, 2) improved mood, 3) increased serotonin levels and 4) increased Natural Killer cell numbers. Women in the relaxation group showed a trend toward improved mood. These preliminary findings are encouraging and provide support for the hypotheses that massage therapy enhances mood and immune function for women with breast cancer.

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## Table of Contents

Cover.....	1
SF 298.....	2
Table of Contents.....	3
Introduction.....	4
Body.....	4-8
Key Research Accomplishments.....	9
Reportable Outcomes.....	10
Conclusions.....	10-11
References.....	12
Appendices.....	

## **Introduction**

Massage therapy has been shown to reduce stress and stress hormones (cortisol), decrease depression and increase serotonergic activity (increased serotonin levels) and positively impact on immune measures, including enhancing Natural Killer (NK) cell numbers and cytotoxicity in adolescents and men with HIV (Diego, et al., 2000; Field, 1998; Ironson et al., 1996). Women with breast cancer are at risk for depression (Longman, Braden & Mishel, 1999; Oktay, 1998; Payne, Hoffmam, Theodulou, Dosik & Massie, 1999), elevated stress and anxiety levels (Farragher, 1998; Oktay, 1998; Payne et al., 1999). Recent studies reveal that elevated anxiety and depression adversely affect immune function in women with breast cancer (Tjemsland, Soreide, Matre & Malt, 1997), as does even mild acute stress (Van der Pompe, Antoni, Visser & Heijnen, 1998). Besides being sensitive to elevated stress levels, cancer patients show a trend for reduced NK cell cytotoxicity (Brittenden, Heys, Ross, & Eremin, 1996). The objectives and specific aims of the ongoing study are to evaluate massage and relaxation therapy effects for an ethnically diverse group of women with early stages of breast cancer (Stages 1 and 2) for 1) decreasing anxiety, stress and stress hormones, 2) decreasing depressed mood and increasing serotonin (a biochemical that diminishes with depression) and 3) boosting immune function (i.e., increasing NK cell number and cytotoxicity). During the course of the three-year study, 60 women diagnosed with Stage 1 and 2 breast cancer will be recruited and assigned to a massage therapy (n=20), a relaxation therapy (n=20) or a control group (n=20). On the first and last day of a 5 week period, self-report measures will be collected on anxiety and depression and women will submit a urine sample and have their blood drawn to assay treatment effects on stress hormones and immune measures.

## **Body**

### **Task 1**

To date we have been successful in screening and training 8 female massage therapists. We have also been successful in developing relations at the breast health center on our medical campus where we have been recruiting participants for the study.

## **Task 2**

We have been successful in screening and recruiting 32 women who met our inclusion/exclusion criteria for Stage 1 or 2 breast cancer.

## **Task 3**

To date we have completed testing for 25 of the 32 women we recruited for Year 1 ( $n=2$  dropped due to attrition). Five women are scheduled to begin testing in September (these women will meet the 3-month post-surgical, chemotherapy, radiation therapy, or reconstructive surgery criteria by their September appointment).

## **Task 4**

We have completed the construction of our data entry spreadsheet, data entry and analyses for the 25 women who have completed the first and last day's measures of the 5-week study. The results of the data analyses completed thus far are summarized below and presented in Table 1. We are missing the biochemistry results for the relaxation group as we were waiting for the ongoing women in that group to complete (the 5 scheduled for September) before sending the batch to be assayed. However, we do have the NK reports for all three groups.

### **Participants**

Twenty-five women ( $M$  age = 53,  $sd$  = 10.4) diagnosed with Stage I or II breast cancer recruited from a university cancer center have completed the protocol. The ethnic distribution was 48% Caucasian, 40% Hispanic and 12% Black. The women were middle to lower middle socioeconomic status ( $M$  = 3.5 on the Hollingshead two-factor index). Participants were matched on support group and age and then randomly assigned to a massage therapy group, relaxation group or standard treatment control group.

### **Results**

On the first and last day's of the study, the women completed two self-report questionnaires to measure their anxiety levels (STAI) and mood (POMS). In addition, they provided urine samples, to

assay for cortisol stress hormone levels and serotonin (5HIAA) values and their blood was drawn to assay NK cell number and cytotoxicity and lymphocytes.

Because of the small sample size, we are reporting means and standard deviations and the results of paired t-tests. By the end of the second year, we should have enough power to conduct multivariate analyses of variances and Bonferroni t-tests.

For the self-report measures, the massage group revealed decreased anxiety (STAI) and improved mood (POMS). The relaxation group (with n=5) is showing a marginal improvement on mood, but this is not significant. For the biochemical measures, the massage therapy group revealed increased 5-HIAA levels, which corresponds with the improved mood. No reduction in stress hormone levels have been observed. The relaxation's group biochemical assays should be available in the fall of this year. For the immune measures, 1) the massage therapy group is showing increased NK cell numbers, 2) the NK cell numbers for the relaxation group is significantly unchanged and 3) the control group is revealing a decline in NK cell numbers. No other measures achieved significance levels. The means and standard deviations for the self-reports, biochemical measures and for the immune assays are reported in Table 1.

### Discussion

The immediate effects of massage therapy for women with breast cancer were decreases in anxiety and depressed mood. Similar massage therapy effects have been reported for other chronic illnesses including HIV (Diego, et al., 2000; Ironson, et al., 1996), multiple sclerosis (Hernandez-Reif, Field, Field & Theakston, 1998), fibromyalgia (Sunshine, Field, et al., 1996) and chronic fatigue syndrome (Field, Sunshine, Hernandez-Reif, et al., 1997). However, the women in the massage therapy group did not show a decrease in cortisol stress hormone levels as has been shown in other studies (Field, Grizzle, et al., 1996; Field, Sunshine, Hernandez-Reif, et al., 1997; Ironson et al., 1996). In relation to the HIV men's study data, the women with breast cancer had higher catecholamine and cortisol values. The men in the HIV men's study received daily massage whereas the women in the present study were massaged 3 times a week. Perhaps more frequent massages or a longer

intervention period is required to decrease cortisol levels for breast cancer patients. Or perhaps with increased numbers (n=20), we will observe the decreased cortisol levels.

The women in the massage therapy group showed increased serotonin levels, which corroborates with their self-reports of improved mood. A reduction in serotonergic activity has been implicated in depression (Weiss, Demetrikopoulos, West & Bonsall, 1998).

Of greatest interest in the current study, and supporting our hypothesis, is the finding that women assigned to massage therapy are showing an increase in NK cell number. The increase in NK cell number supports an earlier HIV men's massage therapy finding (Ironson, Field, et al., 1996) and a recent HIV adolescent girls massage therapy study (Diego, et al., 2000). That massage therapy increased NK cells and that NK cells specialize in destroying virus-infected cells and tumor cells has important implications for massage as an intervention for immune compromised illnesses.

#### Recommended Changes

We are requesting to drop the 6-month follow-up assessment visits because we are finding that the women in the massage therapy group have continued to receive massage treatment on their own accord and therefore the follow-up visits will reflect ongoing treatments, instead of long-term follow-up effects of the 5-week massage program. Ethically, we cannot ask women to refrain from receiving massage after the 5-week treatment period if they are reporting that the treatment is beneficial and they are paying for it out-of-pocket. We would like to replace the follow-up visits with the recruitment of an additional 10-15 women for our mechanism hypothesis that *pressure* on the skin is necessary for the biochemical and immune measure changes we are observing. The new group would involve testing an additional 10-15 women assigned to receive a light pressure massage (sham massage) on the same time schedule as the massage therapy group. The sham massage group would be evaluated on the first and last day of the 5-week study using the same measures we are using for the other three approved groups. This sham massage group would allow us to compare light versus moderate pressure massage effects on the biochemistry and immune response of women with Stage 1 or 2 breast cancer. If the sham massage group does not show changes in the measures, then this

would suggest that 1) the massage effects are not a placebo effect, and 2) massage may be stimulating deep tissue receptor cells, which underlie the cascade of events that lead to the positive changes in the biochemical and immune measures we are observing.



## **Key Research Accomplishments**

- Recruited 32 women with breast cancer in the first year.
- Completed treatment protocol for 25 of the 32 women (5 ongoing and 2 lost to attrition)
- Comparison of 1<sup>st</sup> versus last day's measures for women in the massage therapy group support our hypothesis including:
  - decreased anxiety levels
  - improved mood
  - increased urinary serotonin levels
  - increase in Natural Killer cell numbers

## **Reportable Outcomes**

### **Manuscripts:**

Hernandez-Reif, M., Ironson, G., Field, T., Katz, G., Weiss, S., Fletcher, M., Schanberg, S., & Kuhn, C. (2000). Immunological responses of breast cancer patients to massage therapy ( in preparation).

### **Funding applied for based on work supported by this award:**

NIH R29 grant applied for entitled " Stress, Immunology and Massage Therapy Effects for Aging Women with Breast Cancer" in response to National Institute on Aging (NIA), National Cancer Institute (NCI) and National Institute of Nursing Research (NINR) PA-96-034 AGING WOMEN AND BREAST CANCER. Total direct costs of award applied for \$100,000

## **Conclusions**

The findings thus far include 1) reduced anxiety levels, 2) improved mood , 3) increased urinary serotonin values and 4) increased NK cell numbers for women with early stages of breast cancer receiving massage therapy three times a week (30-minute sessions) over a 5-week period. These findings support the hypothesis that massage therapy effectively attenuates multiple symptoms associated with breast cancer. Future studies might examine potential underlying mechanisms for massage therapy effects, including the hypothesis that pressure might be critical for obtaining the positive findings reported in the first year of this grant.

### **"So What"**

If the findings are substantiated over the 3-year study, then this would suggest that massage therapy is effective for treating women with early stages of breast cancer. Massage therapy may then be offered as an adjunct therapy to attenuate the psychological, biochemical and immune changes associated with the disease. Moreover, massage therapy has little or no side effects, and is a safe

and apparently positive treatment for women with breast cancer in that women in the treatment group continued with the massages on their own accord after the study period. During this resurgence of interest in alternative and complementary medicine, massage therapy provides an effective adjunct treatment for women with breast cancer. Future studies might examine if 1) pressure is required for obtaining the positive effects, 2) if longer treatment durations (e.g., 1 year vs 5 weeks) helps keep the cancer in remission, 3) if massage is effective for later stages of breast cancer or for other cancer forms.

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## APPENDIX

Table 1. Means (standard deviations in parentheses) for the massage therapy, relaxation therapy and control group.

Variables	Massage		Relaxation		Control	
	FIRST Pre/Post	LAST Pre/Post	FIRST Pre/Post	LAST Pre/Post	FIRST Pre/post	LAST Pre/post
<u>Self-reports</u> †						
Anxiety (STAI)	37(14) <sub>a</sub> /27(13) <sub>b</sub> **	35(10) <sub>a</sub> /25(8) <sub>b</sub> **	34(14) <sub>a</sub> /32(12) <sub>a</sub>	38(11) <sub>a</sub> /32(17) <sub>a</sub>	32(9) <sub>a</sub> /30(6) <sub>a</sub>	35(12) <sub>a</sub> /32(9) <sub>a</sub>
Mood (POMS)	12(11) <sub>a</sub> /5(9) <sub>b</sub> **	7(10) <sub>b</sub> /4(7) <sub>b</sub> *	10(18) <sub>a</sub> /7(14) <sub>a</sub>	12(23) <sub>a</sub> /9(18) <sub>a</sub>	9(9) <sub>b</sub> /8(5) <sub>b</sub>	10(10) <sub>b</sub> /7(10) <sub>b</sub>
<u>Biochemical</u>						
Cortisol †	170 (70) <sub>a</sub>	169 (65) <sub>a</sub>			221 (148) <sub>a</sub>	192 (82) <sub>a</sub>
5HIAA ‡	2124 (1505) <sub>a</sub>	3795 (2143) <sub>b</sub> *			3718 (2847) <sub>a</sub>	4054 (3609) <sub>a</sub>
<u>Immune Measures</u> †						
NK Cell	235(129) <sub>a</sub>	263(95) <sub>b</sub> *	337(121) <sub>a</sub>	320(272) <sub>a</sub>	254(90) <sub>a</sub>	236(67) <sub>b</sub> *
NK Activity	27(12.8) <sub>a</sub>	29(13) <sub>a</sub>	31(11) <sub>a</sub>	31(17) <sub>a</sub>	29(13) <sub>a</sub>	30(16) <sub>a</sub>
Lymphocytes	29(4) <sub>a</sub>	32(7) <sub>a</sub>	30(2) <sub>a</sub>	33(4) <sub>a</sub>	30(8) <sub>a</sub>	31(8) <sub>a</sub>

† Lower scores are optimal; ‡ Higher scores are optimal. Different letter subscripts indicate significant differences between adjacent means at the \*  $p < .05$ , \*\*  $p < .01$ .